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DIABETES RESEARCH

STABILIZED HUMAN INSULIN PREVENTS CATHETER OCCLUSION DURING CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

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SUMMARY Obstruction of infusion sets is a major cause of metabolic deterioration or even ketoacidosis during continuous subcutaneous insulin infusion (CSII). 21 type I, CSII-treated patients were studied in a prospective, randomized cross over design during two periods of three months to assess the effects of Genapol® stabilized human insulin (HOE 21 PH H-TRONIN®) on obstruction frequency of PVC catheters in comparison with a neutral preparation of biosynthetic human insulin (BHI). In a total observation time of 9·5 patient-years 79 catheter obstructions by precipitated insulin occurred with an incidence of 0·67 episodes per patient-month for BHI and 0·026 for HOE 21 PH.

Improvement of metabolic control paralleled the reduction of obstruction frequency by HOE 21 PH. Thus, a stabilized insulin preparation is recommended for use in CSII to reduce the therapeutic risk.

Key words: CSII-therapy, catheter occlusion, insulin precipitation, stabilized pump insulin

INTRODUCTION

PORTABLE insulin infusion pumps are increasingly being used in the treatment of insulin-dependent diabetic patients. The devices are designed for continuous subcutaneous infusion of insulin (CSII) through indwelling catheters. Besides local irritation and cutaneous inflammation (1) catheter occlusion by precipitated insulin is a serious complication resulting in loss of metabolic contol (2, 3) or even ketoacidosis (4). Although the problem of insulin aggregation in artificial delivery systems is a well known phenomenon (5), the significance of the type of insulin preparation selected for the use in the infusions devices has been stressed most recently (6). Neutral, buffered, single-peak pork insulin have been found to be superior to an unbuffered, purified porcine (7) insulin preparation or an unbuffered mixture of beef-pork-insulin (6).

In a prospective study we tried to assess the effect of two neutral preparations of human insulin on infusion set obstruction during CSII therapy using pump models with different sizes of the reservoir. One of these formulations has been developed for use in implantable devices (8, 9). The investigation was performed in CSII-treated type I diabetics, in whom the problem of catheter occlusion by precipitated insulin have been frequently seen in the past.

PATIENTS AND METHODS

Twenty-one normal weight patients with a history of at least one catheter occlusion per month were recruited for the study. Informed consent was obtained from all patients. The clinical characteristics, types of insulin pumps and catheters used are indicated in Table 1. The basal rate infusion consisted of 45–51% of the total daily dose and was below 1 U/hr in all cases. Commercially available reservoirs and tubings from the pump manufacturers were used throughout the study. Patients were asked to change the catheter every 48 hr unless an occlusion occurred. Reservoirs had to be replaced when empty. Premarked infusion set wrappers were collected at each visit to ensure the recommended frequency of infusion set change. After skin desinfection the needles were placed in the subcutaneous tissue of the abdominal wall

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Table 1 Patient characteristics

Sex distribution	
women	10/21
men	11/21
Age (yr)	
mean ± SD	32·3 ± 12·1
range	21–52
Duration of diabetes (yr)	
mean ± SD	17 ± 8
range	5 26
Duration of insulin pump therapy (mo)	
mean ± SD	12 ± 3
range	7–18
Insulin pumps	
Autosyringe AS 8 MP (3 ml reservoir)	10/21
CPI Betatron I (1·5 ml reservoir)	2/21
CPI Betatron II (1·5 ml reservoir)	9/21
Catheters (both PVC material)	
Travenol (107 cm)	10/21
CPI (100 cm)	11/21

and fixed with a special tape (Fixomull Stretch, Beiersdorf AG, Hamburg, FRG). Patients performed 4–6 blood glucose measurements per day using a memory-reflectance meter (Glucometer M, Bayer Diagnostic and Electronic). Calculation of MBG values were done by means of the Glucofacts® software (Bayer Diagnostic and Electronic). At four week intervals HbA_1 was determined by a microcolumn method (normal range 5·5 - 8%). Total daily insulin dose was calculated from the patients log books. Occlusion of a catheter was defined by a lack of possibility to rinse the tubing with 0·9% saline or by a visible precipitation in the lumen of the catheter when looking against a dark background. Obstructed catheters were inspected in the ward. Catheters blocked by clotting of blood at the tip of the needle were excluded from the evaluation. All patients had access to medical advice by phone 24 hr a day.

The patients were followed prospectively in a cross-over design. The study protocol included a run-in phase of six weeks, where all the patients used commercially available biosynthetic human insulin (BHI) with a strength of 100 U/ml (Huminsulin® Normal, Eli Lilly, Indianapolis, USA). Then patients were randomly assigned to group A (10 patients), who continued with the same insulin or group B (11 patients), who switched to stabilized, semisynthetic human insulin (Hoe 21 PH, Hoechst AG, Frankfurt, FRG) of the same strength. After three months group A used Hoe 21 PH and group B BHI. During the complete study the same charge of insulin was used. The Hoe 21 PH preparation contains the surface active stabilizer polyethylen-polypropylene-glycol in a concentraion of 10 µg/ml (8). The insulin bottles had different labels, thus the study was not blinded.

Statistical analysis was done by the Wilcoxon- and Student t-test for paired observations as appropriate. Significance was defined by $p < 0.05$. The figures were given in mean ± standard deviation.

Results

From 21 patients entering the study two in group B treated with Betatron II infusion pumps dropped out after four month because of an unacceptable increase of catheter occlusions after change from Hoe 21 PH to BHI and were excluded from the study. Therefore 19 patients completed the protocol over a total observation time of 9·5 patient years or 57 patient-months for each insulin preparation. Each patient experienced at least three episodes of obstruction during the study. While 17 patients had catheter obstructions exclusively with BHI, only two patients observed catheter blockage with both insulin preparations. Throughout the course of the study catheter occlusion occurred 87 times. Clotting of blood in the needle caused obstruction in eight catheters. Thus, catheter occlusion by precipitated insulin was observed with an incidence of 0·69 per patient-month. Seventy-six of these events occurred during treatment with BHI, only three with Hoe 21 PH. The distribution and number of catheter occlusions is given in Table 2.

In spite of different volumes of the reservoir (Travenol: 3 ml, CPI: 1·5 ml) there was no statistical difference in the number of occlusions neither with BHI or Hoe 21 PH (Table 2).

Only in 11 out of 79 events high pressure alarm of the pump preceeded the metabolic deterioration.

Corresponding to the reduction of catheter occlusions a significant improvement of metabolic control could be seen during the treatment with HOE 21 PH (Table 3), while the insulin dose dropped. From the diaries it became obvious, that the reduction of the daily insulin dose was due to insulin given for correction of hyperglycemia following catheter obstruction. Due to frequent blood glucose monitoring no longterm loss of metabolic control or ketoacidosis was observed throughout the study. There was a tendency to minor skin irritations during the use of Hoe 21 PH, but this was not monitored from the beginning.

Discussion

Our study deals with the stability of two neutral preparations of human insulin during clinical use together with polyvinylchloride catheters in CSII treatment. Although not especially designed for insulin delivery, these tubings

Table 2

	Number catheter occlusion					
Insulin preparation	*Group A Travenol/CPI*		*Group B Travenol/CPI*		*Total number*	*Incidence (episode/patient-month)*
BHI	17	23	20	16	76	0·67
Hoe 21 PH	1	1	1	0	3	0·026*

Travenol vs CPI ns in A, 3
* $p < 0.001$.

ble 3 Metabolic control in 19 type I diabetic patients during CSII atment with two insulin preparations

ulin paration	MBG (mg/dl)	HbA_1 (%)	Insulin dose per day (U/day)
II	188 ± 18	9·0 ± 1·2	47·8 ± 6·5
e 21 PH	140 ± 16†	7·7 ± 0·6*	39·1 ± 2·5*

* $p < 0{\cdot}05$.
† $p < 0{\cdot}001$.

re routinely used in pump treated patients and insulin ggregation is a well known fact (2, 3). In our study we elected a group of diabetics, in whom catheter occlusions ıave been seen frequently in the past. Mismanagement or vrong handling of the catheters have been ruled out. In ıddition it has been shown, that patients experience in ɔump therapy seem not to influence the frequency of :athcter occlusions (7). Although not reaching statistical ;ignificance the patients tended to have a lower basal rate .nfusion compared to other pump treated patients at our :linic. Recent investigations have revealed a substantial loss of the preservatives phenol and m-cresol from the insulin solution during perfusion through a plastic catheter of polyvinylchloride (12). This may be one of the reasons for insulin aggregation, when changes of preservative concentration become crucial. The use of buffered pork insulin seemed to overcome the resulting shift of pH in the insulin solution (6). We evaluated highly purified semi-synthetic and biosynthetic human insulin without sodium phosphate buffer. BHI contains 2·5 mg/ml m-cresol, Hoe 21 PH 2·7 mg/ml phenol. Thus, it can be assumed, that loss of preservatives takes place in both formulations.

On the other hand there seems to be a tendency of insulin to aggregate at hydrophobic surfaces (14), which could be overcome by trace amounts of polyethylen-polypropylene-glycol (8). Such insulin formulations have been shown to be stable in implanted devices (9). Our study demonstrated the stability of insulin even in plastic tubings not optimized for insulin infusion systems.

There was a clear cut reduction in catheter occlusions by the stabilized inulin (Hoe 21 PH). In addition there was no influence of the size of the reservoir. A larger volume means a longer stay of the insulin preparation in the reservoir. In the present study the contact of the insulin solution with the inner surface of the catheter seems to be of greater importance for insulin precipitation. Our finding agrees with that of Chawla *et al.* (10), who tested CPI and Travenol reservoirs and infusion sets containing insulin by shaking at 37°C. They found precipitation of insulin in the tubings but not in the syringe reservoirs.

The overall improvement of metabolic control together with a reduction of daily insulin dose is a consequence of reduced frequency of catheter obstruction when stabilized insulin is used. Even under conditions of rather low basal rate the Hoe 21 PH-preparation prevents catheter occlusion by precipitated insulin and the concomitant loss of metabolic control. Thus, in comparison to BHI the formulation Hoe 21 PH is preferable not only for implantable devices but also for use in CSII.

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